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(54) Title: TREATMENT OF COGNITIVE DYSFUNCTIONS'

(57) Abstract: Cognitive dysfunction can be treated by administering to a mammal an effective amount of a compound that is an N-methyl-D-aspartate (NMDA) receptor antagonist and a selective norepinephrine (NE) serotonin (5-HT) reuptake inhibitor (NSRI), most preferably between 1:1 and 20:1 NE:5-HT reuptake. In a preferred embodiment the composition includes a pharmaceutically acceptable carrier and an effective cognition-enhancing amount of milnacipran, most preferably about 25 mg/day to about 250 mg/day. The composition may further include at least one of Ginkgo biloba, Huperzine A, Phosphatidylserine, Vitamin E, Tacrine, Donepezil, Rivastigmine, and Galantamine. The composition can also include at least one of sibutramine, an aminocyclopropane derivative, venlafaxine, duloxetine, desipramine, nortriptyline, protriptyline, amitriptyline, clomipramine, doxepine, imipramine, and trimipramine.

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TREATMENT OF COGNITIVE DYSFUNCTIONS

Background of the Invention

This application claims priority to U.S.S.N. 60/427,767 filed November 20, 2002, U.S.S.N. 60/443,142 filed January 28, 2003, and U.S.S.N. 60/479,761 filed June 18, 2003.

Dementia is an umbrella term for several symptoms related to a decline in thinking skills. Common symptoms include a gradual loss of memory, problems with reasoning or judgment, disorientation, difficulty in learning, loss of language skills, and decline in the ability to perform routine tasks. People with dementia also experience changes in their personalities and behavioral problems, such as agitation, anxiety, delusions (believing in a reality that does not exist), and hallucinations (seeing things that do not exist).

Several disorders that are similar to Alzheimer's disease can cause dementia. These include fronto-temporal dementia, dementia with Lewy bodies, Parkinson's disease, Creutzfeldt-Jakob disease, and Huntington's disease. All of these disorders involve disease processes that destroy brain cells. Vascular dementia is a disorder caused by the disruption of blood flow to the brain. This may be the result of a massive stroke or several tiny strokes.

Some treatable conditions — such as depression, drug interactions, and thyroid problems — can cause dementia. If treated early enough, this

dementia may be effectively treated and even reversed.

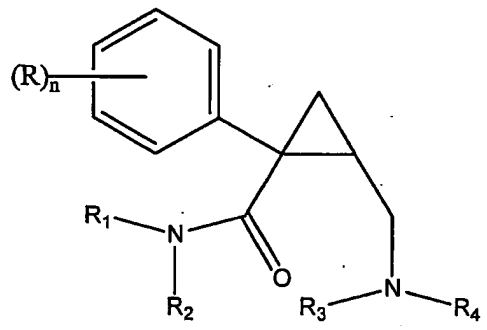
Most dementia are associated with age. Alzheimer's disease is also associated with age. There is no cure for Alzheimer's disease. Mild cognitive impairment (MCI), operationally defined as isolated episodic memory decline, has recently emerged as the clinical entity that most conveniently and reliably represents incipient Alzheimer's disease (AD). *Arch. Neurol.* **58**, 1985-1992 (2001). The risk of conversion to AD is higher in MCI than in the general aged population, as up to 50% of these patients develop the disease within two years. *Neurology* **41**, 1006-1009 (1991). Additionally, MCI is associated with an increased risk of developing dementia: patients develop dementia at a rate of 10-15% per year compared with healthy controls who develop dementia at a rate of 1-2% per year. *Acta. Psychiatr. Scand.* **106**, 403-414 (2002).

There are several drug treatments that may improve or stabilize symptoms and several care strategies and activities that may minimize or prevent behavioral problems. Researchers continue to look for new treatments to alter the course of the disease and other strategies to improve the quality of life for people with dementia. However, drugs that nonspecifically increase noradrenergic activity, such as tricyclic antidepressants, monoamine oxidase inhibitors, amphetamines, and specific norepinephrine reuptake inhibitors, may be detrimental to cognition in neuropsychiatric conditions where PFC functions are compromised.

It is therefore an object of the present invention to provide alternative treatments for various types of cognitive dysfunction.

Summary of the Invention

Cognitive dysfunction can be treated by administering to a mammal an effective amount of a compound that is an N-methyl-D-aspartate (NMDA) receptor antagonist and a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI), most preferably between 1:1 and 20:1 NE:5-HT reuptake. In a preferred embodiment, the pharmaceutical composition includes a pharmaceutically acceptable carrier and an effective cognition-enhancing amount of a compound of formula (I):



(I)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

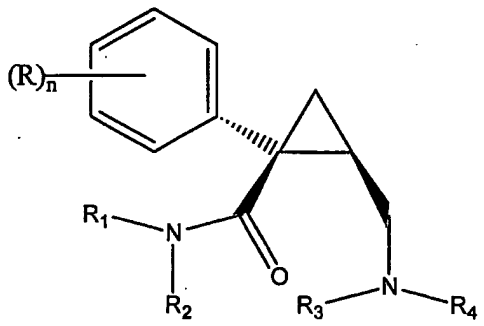
R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

The pharmaceutical composition can include a pharmaceutically acceptable carrier and an effective cognition-enhancing amount of a compound of formula (Ia):



(Ia)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

In a preferred embodiment the composition includes a pharmaceutically acceptable carrier and an effective cognition-enhancing amount of milnacipran, most preferably about 25 mg/day to about 250 mg/day.

The composition may further include at least one of *Ginkgo biloba*, Huperzine A, Phosphatidylserine, Vitamin E, Tacrine, Donepezil, Rivastigmine, and Galantamine. The composition can also include at least one of sibutramine, an aminocyclopropane derivative, venlafaxine, duloxetine, desipramine, nortriptyline, protriptyline, amitriptyline, clomipramine, doxepine, imipramine, and trimipramine.

Brief Description of the Drawings

FIG. 1 is a graph of the time mice took to reach target in the Morris water maze test vs. trial number for mice treated with milnacipran or vehicle.

FIG. 2 shows the total distance traveled by mice to reach the target in the same experiments whose results are shown in FIG. 1.

FIG. 3 shows the percent of time spent by mice in each of the quadrants in the second phase of the Morris water maze test, after the target platform was removed.

Detailed Description of the Invention

As used herein, the following terms and expressions have the indicated meanings. It will be appreciated that the compounds can contain asymmetrically substituted carbon atoms, and can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials.

All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Specifically, for the compound of formula (I), the center bearing both the optionally substituted phenyl ring and the $C(=O)NR_1R_2$ group can be either (R)- or (S)-. The center bearing the hydrogen and the $CH_2NR_3R_4$ can be either (R)- or (S)-. Likewise, for milnacipran, the center bearing both the phenyl ring and the $C(=O)N(CH_2)CH_2$ group can be either (R)-

or (S)-. The center bearing the hydrogen and the CH_2NH_2 group can be either (R)- or (S)-. For the compound of formula (V), the center bearing both the optionally substituted phenyl ring and R_c can be either (R)- or (S)-. The center bearing the R_a and R_b can be either (R)- or (S)-.

Definitions

As used herein, "cognition" refers to the mental process characterized by knowing, thinking, learning, understanding, and judging. See, e.g., Mosby's Medical Dictionary, 5th edition (1998).

As used herein, "cognitive" refers to the mental process of comprehension, judgment, memory, and reasoning, as contrasted with emotional and volitional processes. See, e.g., Mosby's Medical Dictionary, 5th edition (1998).

As used herein, "cognitive function" refers to an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering. See, e.g., Mosby's Medical Dictionary, 5th edition (1998).

As used herein, "cognitive dysfunction" refers to an abnormal or defective cognitive function. Typical cognitive dysfunctions include, e.g., dementia, age-related deficit in cognitive performance, stress-related deficit in cognitive performance, mild cognitive impairment (MCI), schizophrenia, and Alzheimer's disease (AD).

As used herein, "cognitive performance" refers to the ability or capacity of an individual to comprehend, judge, memorize, and reason. The cognitive performance is the capacity of an

individual to become aware of, perceive, or comprehend ideas.

As used herein, "mild cognitive impairment" or "MCI" refers to isolated episodic memory decline.

As used herein, "dementia" is an umbrella term for several symptoms related to a decline in thinking skills. Dementia refers to a general mental deterioration due to organic or psychological factors; characterized by disorientation, impaired memory, judgment, and intellect, and a shallow labile effect. Common symptoms include a gradual loss of memory, problems with reasoning or judgment, disorientation, difficulty in learning, loss of language skills, and decline in the ability to perform routine tasks. People with dementia typically experience changes in their personalities and behavioral problems, such as agitation, anxiety, delusions (believing in a reality that does not exist), and hallucinations (seeing things that do not exist). Specific types of dementia include, e.g., vascular dementia (VaD), dementia of the Alzheimer's type, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia due to Pick's disease, dementia due to Creutzfeldt-Jacob disease, substance-induced persisting dementia, dementia due to multiple etiologies, and global dementia. See, e.g., Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (2000).

As used herein, "dementia of the Alzheimer's type," "Alzheimer's disease," or "AD" refers to a

general mental deterioration due to organic or psychological factors; characterized by disorientation, impaired memory, judgment, and intellect, and a shallow labile effect. See, e.g., Stedman's Medical Dictionary, 11th edition (1990). Alzheimer's disease (AD) is a progressive, degenerative disease of the brain and is one of several disorders that cause the gradual loss of brain cells. Specific types of dementia of the Alzheimer's type include, e.g., dementia of the Alzheimer's type without behavioral disturbance, dementia of the Alzheimer's type with behavior disturbance, dementia of the Alzheimer's type with early onset, and dementia of the Alzheimer's type with late onset. See, e.g., Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (2000).

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric

and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the compounds can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl and cyano. When a substituent is keto (i.e., =O) or thioxo (i.e., =S) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound or an amount of the combination of compounds claimed, e.g., to treat or prevent cognitive dysfunctions or treat the symptoms of cognitive dysfunctions in a host.

"Prodrugs" are intended to include any covalently bonded substances which release the active parent drug or other formulas or compounds *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound, for example milnacipran, are prepared by modifying functional groups present in the compound in such a

way that the modifications are cleaved, either in routine manipulation *in vivo*, to the parent compound. Prodrugs include compounds wherein the hydroxy or amino group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl or free amino, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups.

"Metabolite" refers to any substance resulting from biochemical processes by which living cells interact with the active parent drug or other formulas or compounds *in vivo*, when such active parent drug or other formulas or compounds are administered to a mammalian subject. Metabolites include products or intermediates from any metabolic pathway.

"Metabolic pathway" refers to a sequence of enzyme-mediated reactions that transform one compound to another and provide intermediates and energy for cellular functions. The metabolic pathway can be linear or cyclic. A specific metabolic pathway includes the glucuronide conjugation.

"Milnacipran" or "MIL" refers to (±)-*cis*-2-(aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropanecarboxamide. The CAS Registry Number is 92623-85-3. Methods of preparing milnacipran are disclosed, e.g., in U.S. Patent No. 4,478,836 and references cited therein.

It is believed that that the dextrogyral enantiomer of milnacipran is about twice as active

in inhibiting norepinephrine and serotonin reuptake than the racemic mixture, and that the levrogyral enantiomer is much less potent. See, e.g., Viazzo et al., 1996, *Tetrahedron Lett.* 37(26):4519-4522; Deprez et al., 1998, *Eur. J. Drug Metab. Pharmacokinet.* 23(2): 166-171). Accordingly, milnacipran can be administered in enantiomerically pure form (e.g., the pure dextrogyral enantiomer) or as a mixture of dextrogyral and levrogyral enantiomers, such as a racemic mixture.

The term "N-methyl-D-aspartate (NMDA) receptor antagonist" refers to a compound that binds to and decreases the activity of an NMDA receptor. The term "N-methyl-D-aspartate (NMDA) receptor antagonist" includes both non-competitive and competitive NMDA receptor antagonists. The term "N-methyl-D-aspartate (NMDA) receptor antagonist" includes glycine-site antagonists, glutamate antagonists, and allosteric antagonists. The term "N-methyl-D-aspartate (NMDA) receptor antagonist" includes antagonists of particular subunits, such as NR1 subunits, NR3 subunits, or NR2 subunits, e.g., NR2A, NR2B, NR2C or NR2D subunit antagonists. An antagonist can be selective for a particular subunit type, e.g., a selective NR2B subunit antagonist, or can be a non-selective antagonist of one or more subunit types.

A compound can be determined to be an NMDA receptor antagonist by assays known to those of skill in the art. For instance, a compound can be determined to be an NMDA receptor antagonist by providing protection against NMDA-induced lethality, as assayed in Shuto, S., et al., J. Med.

Chem. 38:2964-2968 (1995). For instance, in particular embodiments, an NMDA receptor antagonist administered at concentrations of 200 mg/kg, 100 mg/kg, 40 mg/kg, or 20 mg/kg shows at least 20% protection against lethality in mice of a 90 mg/kg injection of NMDA.

A compound can also be determined to be an NMDA receptor antagonist by competition for binding to an NMDA receptor or receptor subunit against a known NMDA receptor agonist or antagonist, as determined using assays known to persons of skill in the art and described in the references cited herein, provided the compound inhibits NMDA receptor activity.

An NMDA receptor antagonist may compete with phenylcyclidine (PCP) for binding to the NMDA receptor, as described and assayed in Page et al., FEBS Letters 190:333 (1985). An NMDA receptor antagonist that competes with PCP for binding to the NMDA receptor is a "PCP-site NMDA receptor antagonist."

An NMDA receptor antagonist may compete with polyamines for binding to the NMDA receptor, as described and assayed in Shoemaker, H. et al., Eur. J. Pharmacol. 176:249-250 (1990). An NMDA receptor antagonist that competes with a polyamine for binding to the NMDA receptor is a "polyamine-site NMDA receptor antagonist."

An NMDA receptor antagonist may compete with glycine for binding to the NMDA receptor, as described and assayed in Mugnaini, M., et al., Eur. J. Pharmacol. 391:233 (2000). An NMDA receptor antagonist that competes with glycine for binding

to the NMDA receptor is a "glycine-site NMDA receptor antagonist."

The terms "serotonin (5-HT) reuptake" and "norepiniphrine (NE) reuptake" refer to the uptake of the 5-HT or NE from the synaptic cleft by a presynaptic neuron after release of the neurotransmitter by the same neuron in synaptic transmission. The original release of the neurotransmitter into the synaptic cleft by the presynaptic neuron triggers an action potential in the postsynaptic neuron. Reuptake of the neurotransmitter allows the resting potential of the postsynaptic neuron to be restored, clearing the way for it to receive another transmission.

The term "selective serotonin (5-HT) reuptake inhibitor" refers to a compound that has an IC_{50} for sodium-dependent 5-HT reuptake into rat cerebral cortical synaptosomes of 200 nM or less, and an IC_{50} for sodium-dependent dopamine uptake into rat striatum synaptosomes of at least 1000 nM, as assayed in Mochizuki, D., et al., Psychopharmacology 162:323-332 (2002). Assays for 5-HT reuptake inhibition activity can also be conducted with recombinant human 5-HT transporter expressed in a cell line in vitro, such as the LLC-PK1 cell line, as reported in Gu et al. J. Biol. Chem. 269:7124-7130 (1994).

In a specific embodiment, the IC_{50} for 5-HT reuptake is 100 nM or less, and for dopamine reuptake is 5 μM or more.

The term "selective norepinephrine (NE) reuptake inhibitor" refers to a compound that has an IC_{50} for sodium-dependent NE reuptake into rat

cerebral cortical synaptosomes of 200 nM or less, and an IC_{50} for sodium-dependent dopamine uptake into rat striatum synaptosomes of at least 1000 nM, as assayed in Mochizuki, D., et al., Psychopharmacology 162:323-332 (2002). In a specific embodiment, the IC_{50} for NE reuptake is 100 nM or less, and for dopamine reuptake is 5 μM or more.

In particular embodiments, the selective NE reuptake inhibitor also has an IC_{50} for sodium-dependent 5-HT reuptake of 300 nM or greater, or of 1000 nM or greater.

The term "selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI)" refers to a compound that is both a selective NE reuptake inhibitor and a selective 5-HT reuptake inhibitor. Specifically, an NSRI has an IC_{50} for 5-HT reuptake of 200 nM or less and an IC50 for NE reuptake of 200 nM or less, and an IC_{50} for dopamine reuptake of at least 1000 nM. The NSRI will have an NE:5-HT reuptake inhibition ratio of at least about 0.5:1. The NE:5-HT reuptake inhibition ratio is calculated by dividing the IC_{50} for 5-HT reuptake by the IC_{50} for NE reuptake. For instance, if a compound has an IC_{50} for NE reuptake of 10 nM and an IC_{50} for 5-HT reuptake of 20 nM, it has an NE:5-HT reuptake inhibition ratio of 2:1. In specific embodiments, the NSRI will have an NE:5-HT reuptake inhibition ratio of about 0.5:1 to about 20:1, about 1:1 to about 20:1, about 0.5:1 to 5:1, about 1:1 to about 5:1, about 0.5:1 to about 3:1, or about 1:1 to about 3:1.

In specific embodiments, the NSRI has an IC50 for sodium-dependent dopamine reuptake of at least 5 μM.

Various techniques are known to determine the norepinephrine (NE) - serotonin (5-HT) reuptake inhibition of a particular NSRI. In one embodiment, the ratio can be calculated from IC_{50} data for NE and 5-HT reuptake inhibition. For example, it has been reported that for milnacipran the IC_{50} of norepinephrine reuptake is 100 nM, whereas the IC_{50} serotonin reuptake inhibition is 200 nM. See, Moret et al., Neuropharmacology, 24(12):1211-1219, 1985; Palmier, C., C. Puozzo, et al. (1989). "Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran." Eur J Clin Pharmacol **37**(3): 235-8.

The NE:5-HT reuptake inhibition ratio for milnacipran based on this data is 2:1. Other IC values such as IC_{25}, IC_{75}, etc. could be used, provided the same IC value is compared for both norepinephrine and serotonin. The concentrations necessary to achieve the desired degree of inhibition (i.e., IC value) can be calculated using known techniques either *in vivo* or *in vitro*. See, Sanchez, C. and J. Hyttel (1999). "Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding." Cell Mol Neurobiol **19**(4): 467-89; Turcotte, J. E., G. Debonnel, et al. (2001). "Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects." Neuropsychopharmacology **24**(5):

511-21; Moret, C., M. Charveron, et al. (1985). "Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl- aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug." Neuropharmacology **24**(12): 1211-9; Moret, C. and M. Briley (1997). "Effects of milnacipran and pindolol on extracellular noradrenaline and serotonin levels in guinea pig hypothalamus." J Neurochem **69**(2): 815-22; Bel, N. and F. Artigas (1999). "Modulation of the extracellular 5-hydroxytryptamine brain concentrations by the serotonin and noradrenaline reuptake inhibitor, milnacipran. Microdialysis studies in rats." Neuropsychopharmacology **21**(6): 745-54; and Palmier, C., C. Puozzo, et al. (1989). "Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran." Eur J Clin Pharmacol **37**(3): 235-8.

The term "noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist" refers to a compound that does not compete with NMDA for binding to the receptor. That is, the receptor can bind both NMDA and the noncompetitive antagonist at the same time. Whether an antagonist is noncompetitive can be determined by conventional inhibition kinetics studies, as is well known in the art. See, e.g., Zubay and Breslow, pages 259-283, in Geoffrey Zubay, Biochemistry, second edition, (1988), Macmillan, New York.

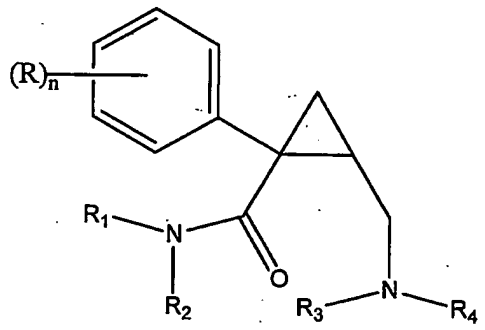
Preferred NSRIs

A preferred absolute stereochemistry on the carbon atom of the compound of formula (I), bearing

both the optionally substituted phenyl ring and the $C(=O)NR_1R_2$ group, is (R)- . Another preferred absolute stereochemistry on the carbon atom of the compound of formula (I), bearing both the optionally substituted phenyl ring and the $C(=O)NR_1R_2$ group is (S)- .

A preferred absolute stereochemistry on the carbon atom of the compound of formula (I), bearing the hydrogen and the $CH_2NR_3R_4$ group is (R)-. Another preferred absolute stereochemistry on the carbon atom of the compound of formula (I), bearing the hydrogen and the $CH_2NR_3R_4$ group is (S)-.

Formula (I):



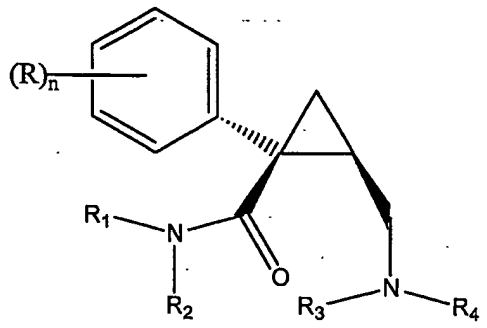
(I)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein, R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino; n is 1 or 2; R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted

heterocycle; or R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom; R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

The NE:5-HT of milnacipran is about 2:1. See, Moret, C., M. Charveron, et al. (1985). "Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl- aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug." Neuropharmacology **24**(12): 1211-9.) Palmier, C., C. Puozzo, et al. (1989). "Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran." Eur J Clin Pharmacol **37**(3): 235-8. Milnacipran and synthetic preparations of the same are described in U.S. Patent 4,478,836, and references cited therein. Additional information regarding milnacipran may be found in the Merck Index, 12th Edition, at entry 6281.

Another embodiment is where the compound is a compound of formula (Ia):

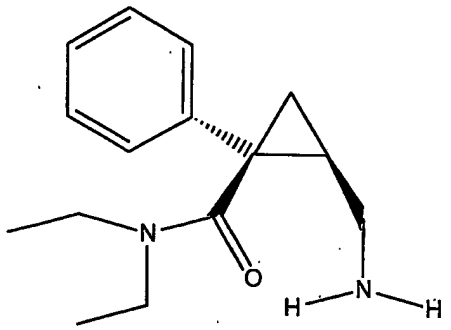


(Ia)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein, R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino; n is 1 or 2; R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom; R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

In another embodiment R is hydrogen. In another embodiment n is 1. In still another embodiment R_1 is alkyl and in particular R_1 is ethyl. In yet another embodiment R_2 is alkyl and in particular R_2 is ethyl. In still another embodiment R_3 is hydrogen and/or R_4 is hydrogen.

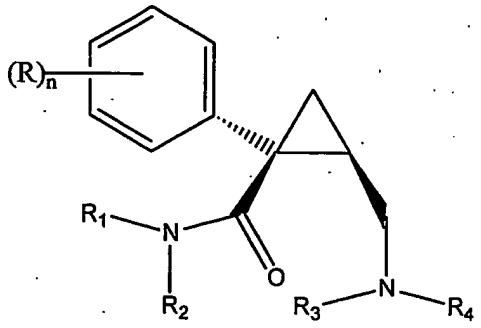
In a preferred embodiment the compound is milnacipran a compound of the formula:



or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof.

In preferred embodiment the N-methyl-D-aspartate (NMDA) receptor antagonist is not CGP 37-849, MK-801, or AP7; as disclosed in Behav. Neural. Biol. 60 p 224- (1993) and Exp. Brain Research 75 p 449 - (1989).

Another embodiment includes a pharmaceutically acceptable carrier and an effective cognition-enhancing amount of a compound of formula (Ia):

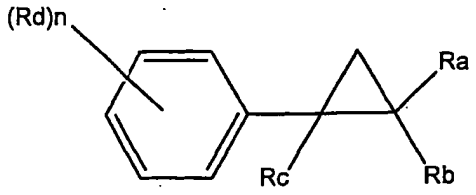


(Ia)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino; n is 1 or 2; R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom; R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

Additional compounds that act as an N-methyl-D-aspartate (NMDA) receptor antagonist, a dual selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) and selective norepinephrine reuptake inhibitor (NERI), or a combination thereof, include compounds of formula (V):



(V)

wherein R_a is hydrogen, alkyl, substituted alkyl, $COOR_e$ or NR_eR_e; wherein each R_e is independently hydrogen, alkyl, or substituted alklyl; R_b is hydrogen, alkyl, substituted alkyl, $COOR_e$ or NR_eR_e; wherein each R_e is independently hydrogen, alkyl, or substituted alklyl; or R_b together with R_c forms an alkylene chain or a substituted alklylene chain; R_c is hydrogen, alkyl, substituted alkyl, $COOR_e$ or NR_eR_e; wherein each R_e is independently hydrogen, alkyl, or substituted alklyl; or R_c together with R_b forms an alkylene chain or a substituted alklylene chain; R_d is hydrogen, halo, hydroxy, alkoxy, nitro, $COOR_e$ or NR_eR_e; wherein each R_e is independently hydrogen, alkyl, or substituted alklyl; n is 1, 2, 3, 4, or 5; or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof.

Examples of compounds of formula (V):

A specific value for R_a is hydrogen, COOH, or CH_2NH_2.

A specific value for R_b is hydrogen, COOH, CH_2NH_2, or together with Rc forms a $-CH_2NHC(=O)-$ chain, or a $-CH_2OC(=O)-$ chain.

A specific value for R_c is $C(=O)N(CH_2NH_2)CH_2NH_2$, $C(=O)N(H)CH_2NH_2$, $C(=O)OH$, or together with R_b forms a $-CH_2NHC(=O)-$ chain, or a $-CH_2OC(=O)-$ chain.

A specific value for R_d is hydroxy.

A specific value for n is 1.

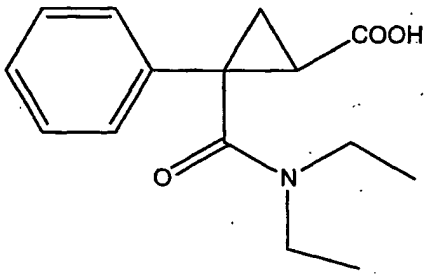
A specific value for $(R_d)_n$ is para-hydroxy.

A preferred absolute stereochemistry on the carbon atom of the compound of formula (V), bearing the optionally substituted phenyl ring and R_c is (R)-. Another preferred absolute stereochemistry

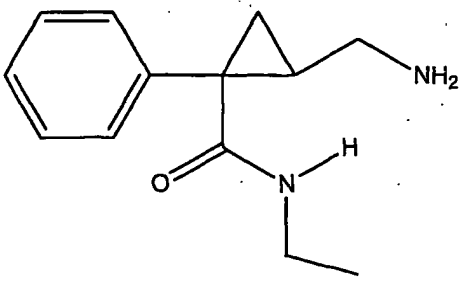
on the carbon atom of the compound of formula (V), bearing the optionally substituted phenyl ring and R_c is (S)-.

A preferred absolute stereochemistry on the carbon atom of the compound of formula (V), bearing R_a and R_b is (R)-. Another preferred absolute stereochemistry on the carbon atom of the compound of formula (V), bearing R_a and R_b is (S)-.

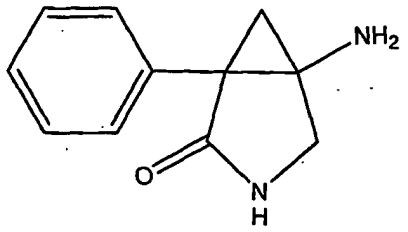
Additional specific compounds that act as an N-methyl-D-aspartate (NMDA) receptor antagonist, a dual selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) and selective norepinephrine reuptake inhibitor (NERI), or a combination thereof include compounds of formula (VI)-(XV):



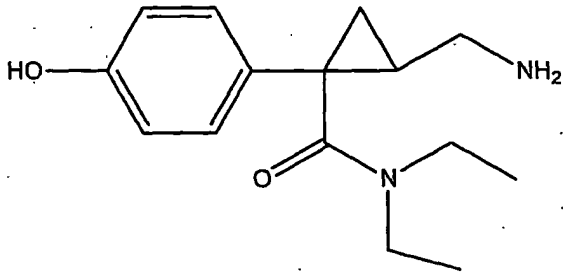
(VI)



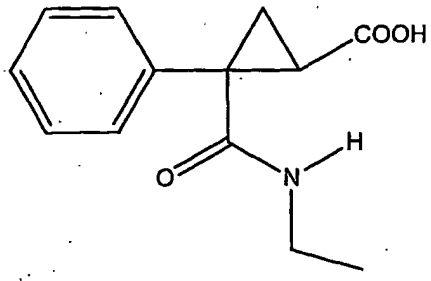
(VII)



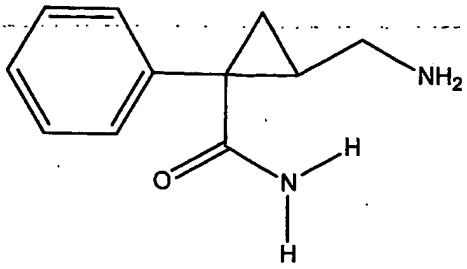
(VIII)



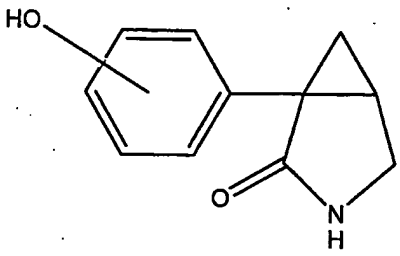
(IX)



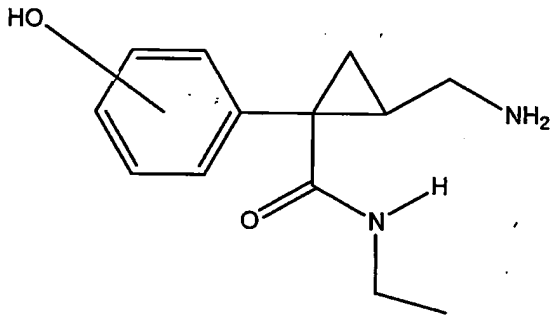
(X)



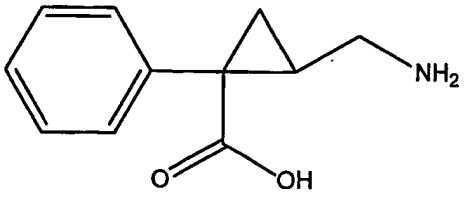
(XI)



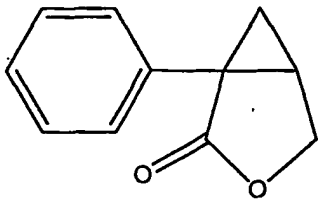
(XII)



(XIII)



(XIV)



(XV)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof.

Specific embodiments administer an effective amount of a compound that is an N-methyl-D-aspartate (NMDA) receptor antagonist, wherein the compound is also a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI), a selective norepinephrine reuptake inhibitor (NERI), or a combination thereof. In another embodiment the N-methyl-D-aspartate (NMDA) receptor antagonist has a dissociation constant with the NMDA receptor of 50 micromolar (μM) or less. In still another embodiment the N-methyl-D-aspartate (NMDA) receptor antagonist has a dissociation constant with the NMDA receptor of 20 micromolar (μM) or less. Another embodiment is where the N-methyl-D-aspartate (NMDA) receptor antagonist is a non-competitive NMDA receptor antagonist, a competitive NMDA receptor antagonist, a glycine-site antagonist, a glutamate-site antagonist, an NR1 subunit antagonist, an antagonist of an NR2

subunit, (e.g., an NR2A-, NR2B, NR2C, or NR2-D antagonist), or an NR3 subunit antagonist. The antagonists of particular subunits may be selective or non-selective. In still another embodiment, the NMDA receptor antagonist is a PCP-site NMDA receptor antagonist. In yet another embodiment, the selective norepinephrine reuptake inhibitor (NERI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from cerebral cortex of 1 micromolar (μM) or less. In still another embodiment, the selective norepinephrine reuptake inhibitor (NERI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from cerebral cortex of 100 nanomolar (nM) or less. In yet another embodiment the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 20:1, about 1 : 1 to about 5:1, or about 1 : 1 to about 3:1. The selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) is selected to have limited post-synaptic receptor effects, such that the ki at each of adrenergic and cholinergic sites is greater than about 500 nanomolar (nM).

Another embodiment provides a pharmaceutical composition that includes a pharmaceutically acceptable carrier, an effective cognition-enhancing amount of milnacipran, and at least one of *Ginkgo biloba*, Huperzine A, Phosphatidylserine, Vitamin E, Tacrine, Donepezil, Rivastigmine, and Galantamine. Another embodiment provides a pharmaceutical composition that includes a pharmaceutically acceptable carrier, an effective cognition-enhancing amount of milnacipran, and at

least one of sibutramine, an aminocyclopropane derivative, venlafaxine, duloxetine, desipramine, nortriptyline, protriptyline, amitriptyline, clomipramine, doxepine, imipramine, and trimipramine.

Ginkgo biloba

Ginkgo biloba is a plant extract containing several compounds that may have positive effects on cells within the brain and the body. *Ginkgo biloba* is thought to have both antioxidant and anti-inflammatory properties, to protect cell membranes, and to regulate neurotransmitter function. *Ginkgo* has been used for centuries in traditional Chinese medicine and currently is being used in Europe to alleviate cognitive symptoms associated with a number of neurological conditions.

In a study published in the *Journal of the American Medical Association* (October 22/29, 1997), Pierre L. Le Bars, MD, PhD, of the New York Institute for Medical Research, and his colleagues observed in some participants a modest improvement in cognition, activities of daily living (such as eating and dressing), and social behavior. The researchers found no measurable difference in overall impairment.

Results from this study show that ginkgo may help some individuals with Alzheimer's disease. Few side effects are associated with the use of *Ginkgo*, but it is known to reduce the ability of blood to clot, potentially leading to more serious conditions, such as internal bleeding. This risk may increase if *Ginkgo biloba* is taken in

combination with other blood-thinning drugs, such as aspirin and warfarin.

Huperzine A

Huperzine A is a moss extract that has been used in traditional Chinese medicine for centuries. Because it has properties similar to those of FDA-approved Alzheimer medications, it is promoted as a treatment for Alzheimer's disease. Evidence shows that the effectiveness of huperzine A may be comparable to that of the approved drugs. Alzheimer's Association website, October 31, 2002 (http://www.alz.org).

Phosphatidylserine

Phosphatidylserine is a kind of lipid, or fat, that is the primary component of cell membranes of neurons. In Alzheimer's disease and similar disorders, neurons degenerate for reasons that are not yet understood. The strategy behind the possible treatment with phosphatidylserine is to shore up the cell membrane and possibly protect cells from degenerating. Alzheimer's Association website, October 31, 2002 (http://www.alz.org)

Vitamin E

Vitamin E supplements are often prescribed as a treatment for Alzheimer's disease, because they may help brain cells defend themselves from "attacks." Normal cell functions create a byproduct a called free radical, a kind of oxygen molecule that can damage cell structures and genetic material. This damage, called oxidative stress, may play a role in Alzheimer's disease.

Cells have natural defenses against this damage, including the antioxidants vitamins C and

E, but with age some of these natural defenses decline. Research has shown that taking vitamin E supplements may offer some benefit to people with Alzheimer's.

Most people can take vitamin E without side effects. A person taking "blood-thinners," however, may not be able to take Vitamin E or will need to be monitored closely by a physician.

Cholinesterase Inhibitors

Currently, there are four drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's disease: Tacrine (Cognex®), Donepezil (Aricept®), Rivastigmine (Exelon®), and Galantamine (Reminyl®). These four medications are in a class of drugs known as cholinesterase inhibitors. They are designed to prevent the breakdown of acetylcholine, a chemical messenger in the brain that is important for memory and other thinking skills. The drugs work to keep levels of the chemical messenger high, even while the cells that produce the messenger continue to become damaged or die. About half of the people who take cholinesterase inhibitors experience a modest improvement in cognitive symptoms.

As used herein, Tacrine (Cognex®) refers to 1,2,3,4-tetrahydro-9-acridinamine or 9-amino-1,2,3,4-tetrahydro-5-aminoacridine. See, e.g., Merck Index (11th edition) and *N. Engl. J. Med.* **315**, 1241 (1986).

As used herein, Donepezil (Aricept®) refers to (±)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride. See, e.g., USP Dictionary (2000 edition).

As used herein, Rivastigmine (Exelon®) refers to (S)-3-[1-(dimethylamino)ethyl]phenyl ethylmethylcarbamate. See, e.g., USP Dictionary (2000 edition).

As used herein, Galanthamine (Reminyl®) refers to 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol. See, e.g., Merck Index (11th edition) and *J. Chem. Soc.* 806, (1962).

Treatment of Cognitive Dysfunction

These agents are useful for the treatment of cognitive dysfunctions and related diseases and symptoms. For example, the compounds may be used to treat dementia, age-related deficit in cognitive performance, stress-related deficit in cognitive performance, mild cognitive impairment (MCI), schizophrenia, Alzheimer's disease (AD), or symptoms associated thereof. In another embodiment, the dementia is vascular dementia (VaD), dementia of the Alzheimer's type, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia due to Pick's disease, dementia due to Creutzfeldt-Jacob disease, substance-induced persisting dementia, dementia due to multiple etiologies, or global dementia. In still another embodiment the dementia of the Alzheimer's type is dementia of the Alzheimer's type without behavioral disturbance, dementia of the Alzheimer's type with behavior disturbance, dementia of the Alzheimer's type with early onset, or dementia of the Alzheimer's type with late onset.

In a preferred embodiment, the method includes administering to the mammal an effective amount of a compound that is an N-methyl-D-aspartate (NMDA) receptor antagonist, wherein the compound is a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI), a selective norepinephrine reuptake inhibitor (NERI), or a combination thereof.

The compounds are also useful as standard or reference compounds for use in tests or assays for determining the ability of an agent to treat, prevent, or lessen the conditions or symptoms associated with cognitive dysfunction, for example in a pharmaceutical research program. Thus, the compounds disclosed herein may be used as control or reference compound in such assays and as a quality control standard. The compounds may be provided in a commercial kit or container for use as such standard or reference compound. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but preferably are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent

treatment; the frequency of treatment; and the effect desired. Dosage forms of compositions suitable for administration contain from about 20 mg to about 500 mg of active ingredient per unit. The active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

In a preferred embodiment, milnacipran is administered up to about 400 mg/day. In another embodiment, milnacipran is administered in a dosage of about 25 mg/day to about 250 mg/day.

The composition is preferably administered one or more times a day, or in a sustained and/or delayed release formulation to provide effective drug dosages all day long.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms. Additives may also be included in the formulation to enhance the physical appearance, improve stability, and aid in disintegration after administration. For example, liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release

products to provide for continuous release of medication over a period of hours or days. Sustained release products can also be formulated for implantation or transdermal/transmucosal delivery. Such formulations typically will include a polymer that biodegrades or bioerodes thereby releasing a portion of the active ingredient. The formulations may have the form of microcapsules, liposomes, solid monolithic implants, gels, viscous fluids, discs, or adherent films. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Compressed tablets can be formulated to release the drug substance in a manner to provide medication over a period of time. There are a number of types which include delayed-action tablets in which the release of the drug substance is prevented for an interval of time after administration or until certain physiological conditions exist; repeat-action tablets which periodically release a complete dose of the drug substance to the gastrointestinal fluids; and the extended-release tablets which continuously release increments of the contained drug substance to the gastrointestinal fluids.

Typically, water, suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water-soluble

salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences, supra*, a standard reference text in this field.

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. These include (1) diluents, (2) binders, and (3) lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are (1) disintegrators, (2) colors, and in the case of chewable tablets, (3) flavors, and (4) sweetening agents.

Pharmaceutical kits useful for the treatment for cognitive dysfunctions, and related diseases and symptoms, which include a therapeutically effective amount of a pharmaceutical composition that includes a compound of component (a) and one or more compounds of component (b), in one or more sterile containers. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in separate sterile

containers. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as desired. Component (a) and component (b) may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

The following examples are introduced in order that the invention may be more readily understood. They are intended to illustrate the invention but not limit its scope.

Example 1: Assessment of Milnacipran and citalopram on spatial memory.

These experiments assess the effects of two different antidepressants - milnacipran and citalopram -- on a spatial memory task in young adult C57BL/6 and BALB/c mice.

Methods

Adult male C57BL/6 mice and BALB/c mice (12 weeks) were injected i.p. x2 daily (07:00 and 19:00 hr) with vehicle or doses of the test compounds. Animals were injected for 2 weeks prior to the initiation of the behavioral training, and subsequently throughout the training and testing

procedures. A standard Morris water maze protocol was used. See D'Hooge, R., et al., Brain Research Reviews 36:60-90 (2001). The apparatus consisted of a 1.2 m diameter pool that was 28 cm in height and filled with 22°C opaque colored water to a depth of 22 cm. The pool was surrounded by distinct fixed visual cues that the mice can use to navigate to the escape platform. Clear Plexiglas platforms were used for the training phases of the experiments. Initial training used a platform that is exposed 0.5 cm above the water, and is flagged, so that the mice could recognize that an escape response is possible. The location of the platform was varied over the 4 trials in order to prevent any habituation to the platform position. Animals then went through a 5-day acquisition phase where a platform is submerged 0.5 cm below the water level and placed in the middle of one of the 4 predefined quadrants. In each trial, mice were given 60 seconds to find the escape platform. Mice that were unable to escape within the 60 seconds were guided to the platform. All animals were allowed to rest on the platform for 20 seconds. Trajectories were monitored with a computerized video tracking system (San Diego Instruments). Swim paths and latencies to locate the platform were evaluated. A technician blinded to the experimental treatments analyzed the data.

The second phase of the testing began the day after the last acquisition trial and consisted of 4 probe trials. The platform was removed from the water tank and the animal was placed into the water for 1 min. Data was collected by the video tracking

system and time spent in the 4 quadrants was analyzed along with path tracings.

All training sessions and behavioral testing took place from 10:00 to 17:00 hours. The doses of each tested compound were based on published doses in the literature.

The tested compounds were milnacipran (10 mg/kg twice daily or 30 mg/kg twice daily; and citalopram, a selective 5-HT reuptake blocker (1 mg/kg, 10 mg/kg, 30 mg/kg or 45 mg/kg i.p. for acute; and 1 mg/kg or 10 mg/kg i.p. for chronic).

Results:

Figure 1 shows the time to reach the target in the first phase of testing for BALB/c mice treated with control vehicle or milnacipran on each of the five days of the acquisition trials. The time to target decreased more for the mice treated with 30 mg/kg milnacipran than for control mice, and decreased even more over the course of the trial for mice treated with the lower dose of 10 mg/kg. This demonstrated that milnacipran enhanced memory and learning performance in this task. In contrast, mice treated with citalopram performed no better on this test than mice treated with the vehicle control.

Figure 2 shows the total distance traveled in the pool by the BALB/c mice treated with each of the two doses of milnacipran over the 5 days of acquisition trials in the Morris water maze tests, as they searched for the platform. By this measure, the 30 mg/kg dose may have been slightly superior to the 10 mg/kg dose in enhancing memory and learning.

Figure 3 shows the results of the second phase of testing, where the platform is removed and time spent in each of the four quadrants by the mice in the pool lacking the platform is measured. Mice with enhanced memory should spend more time in the one quadrant where the platform had been (quadrant 2). This test showed that BALB/c mice treated with milnacipran spent approximately 50% or more of their time in quadrant 2, indicating a clear memory of the quadrant where the platform had been. Mice treated with vehicle spent approximately equal time in all quadrants. Thus, this test also showed that milnacipran enhanced spatial memory and learning. Data in this test with BALB/c mice treated with citalopram did not differ from mice treated with vehicle control.

In contrast to the BALB/c mice, cognitive enhancement in the C57BL/6 strain could not be demonstrated, due to superior performance by this strain compared to the BALB/c strain.

The results demonstrate that chronic treatment with milnacipran has beneficial effects on cognitive performance in a high anxiety strain of mice (BALB/c).

We claim:

1. A method of treating a cognitive dysfunction in a mammal, the method comprising administering to the mammal an effective amount of a compound that is an N-methyl-D-aspartate (NMDA) receptor antagonist and a selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) having a ratio of between 1:1 and 20:1.

2. The method of claim 1 wherein the N-methyl-D-aspartate (NMDA) receptor antagonist has a dissociation constant with the NMDA receptor of 50 micromolar (μM) or less.

3. The method of claim 1 wherein the N-methyl-D-aspartate (NMDA) receptor antagonist has a dissociation constant with the NMDA receptor of 20 micromolar (μM) or less.

4. The method of claim 1 wherein the N-methyl-D-aspartate (NMDA) receptor antagonist is a non-competitive NMDA receptor antagonist, a competitive NMDA receptor antagonist, a glycine-site antagonist, a glutamate-site antagonist, an NR1 subunit antagonist, an antagonist of an NR2 subunit, or an NR3 subunit antagonist.

5. The method of claim 1 wherein the NMDA receptor antagonist is a PCP-site NMDA receptor antagonist.

6. The method of claim 1 wherein the selective norepinephrine reuptake inhibitor (NERI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from cerebral cortex of 1 micromolar (μM) or less.

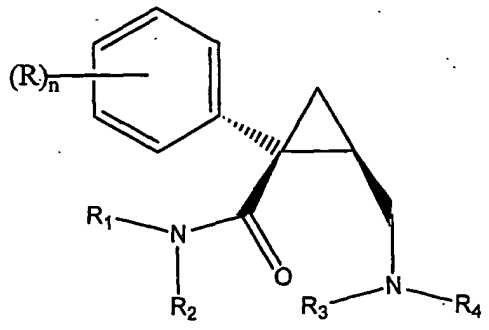
7. The method of claim 1 wherein the selective norepinephrine reuptake inhibitor (NERI) has an IC_{50} for inhibition of noradrenaline reuptake into synaptosomes from cerebral cortex of 100 nanomolar (nM) or less.

8. The method of claim 1 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 5:1.

9. The method of claim 1 wherein the selective NSRI has an NE : 5-HT reuptake inhibition ratio of about 1 : 1 to about 3:1.

10. The method of claim 1 wherein the selective norepinephrine (NE) - serotonin (5-HT) reuptake inhibitor (NSRI) has limited post-synaptic receptor effects, such that the ki at each of adrenergic and cholinergic sites is greater than about 500 nanomolar (nM).

11. The method of claim 1 wherein the compound is a compound of formula (Ia):



(Ia)

or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof wherein,

R is independently hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, hydroxy, nitro, amino, or substituted amino;

n is 1 or 2;

R_1 and R_2 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, alkaryl, substituted alkaryl, heteroaryl, substituted heteroaryl, heterocycle, or substituted heterocycle; or

R_1 and R_2 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom;

R_3 and R_4 are each independently hydrogen, alkyl, or substituted alkyl; or

R_3 and R_4 can form a heterocycle, substituted heterocycle, heteroaryl, or substituted heteroaryl with the adjacent nitrogen atom.

12. The method of claim 11 wherein R is hydrogen.

13. The method of claim 11 wherein n is 1.

14. The method of claim 11 wherein R_1 is alkyl.

15. The method of claim 11 wherein R_1 is ethyl.

16. The method of claim 11 wherein R_2 is alkyl.

17. The method of claim 11 wherein R_2 is ethyl.

18. The method of claim 11 wherein R_3 is hydrogen.

19. The method of claim 11 wherein R_4 is hydrogen.

20. The method of claim 11 wherein the compound is milnacipran or sterioisomeric forms, mixtures of sterioisomeric forms, or pharmaceutically acceptable salts thereof.

21. The method of claim 20 wherein the compound of the formula recited therein (milnacipran) is

administered in about 25 mg/day to about 250 mg/day.

22. The method of claim 1 wherein the cognitive dysfunction is dementia, age-related deficit in cognitive performance, stress-related deficit in cognitive performance, mild cognitive impairment (MCI), schizophrenia, Alzheimer's disease (AD), or symptoms associated thereof.

23. The method of claim 22 wherein the dementia is vascular dementia (VaD), dementia of the Alzheimer's type, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia due to Pick's disease, dementia due to Creutzfeldt-Jacob disease, substance-induced persisting dementia, dementia due to multiple etiologies, or global dementia.

24. The method of claim 22 wherein the dementia of the Alzheimer's type is dementia of the Alzheimer's type without behavioral disturbance, dementia of the Alzheimer's type with behavior disturbance, dementia of the Alzheimer's type with early onset, or dementia of the Alzheimer's type with late onset.

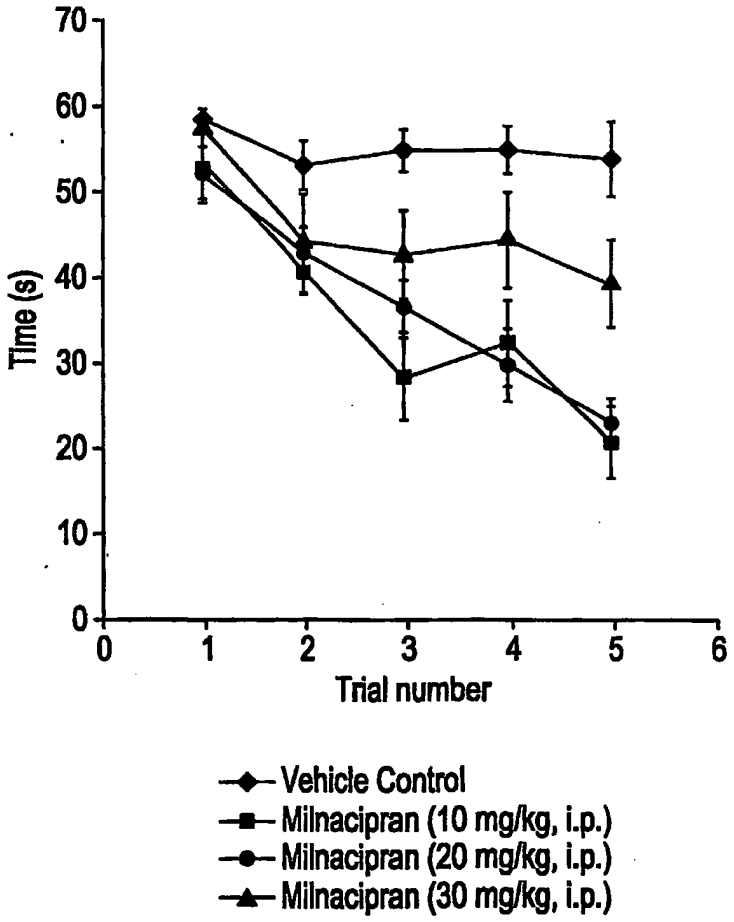
25. The method of claim 1 further comprising administering at least one of *Ginkgo biloba*, Huperzine A, Phosphatidylserine, Vitamin E, Tacrine, Donepezil, Rivastigmine, and Galantamine.

26. The method of claim 1 further comprising administering an effective cognition-enhancing amount of milnacipran, and at least one of sibutramine, an aminocyclopropane derivative, venlafaxine, duloxetine, desipramine,

nortriptyline, protriptyline, amitriptyline, clomipramine, doxepine, imipramine, and trimipramine.

27. A pharmaceutical composition or kit for use in the method of any of claims 1-26.

FIG. 1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20
10
0
Time (s)
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1
2
3
4
5
6
Trial number
Vehicle Control
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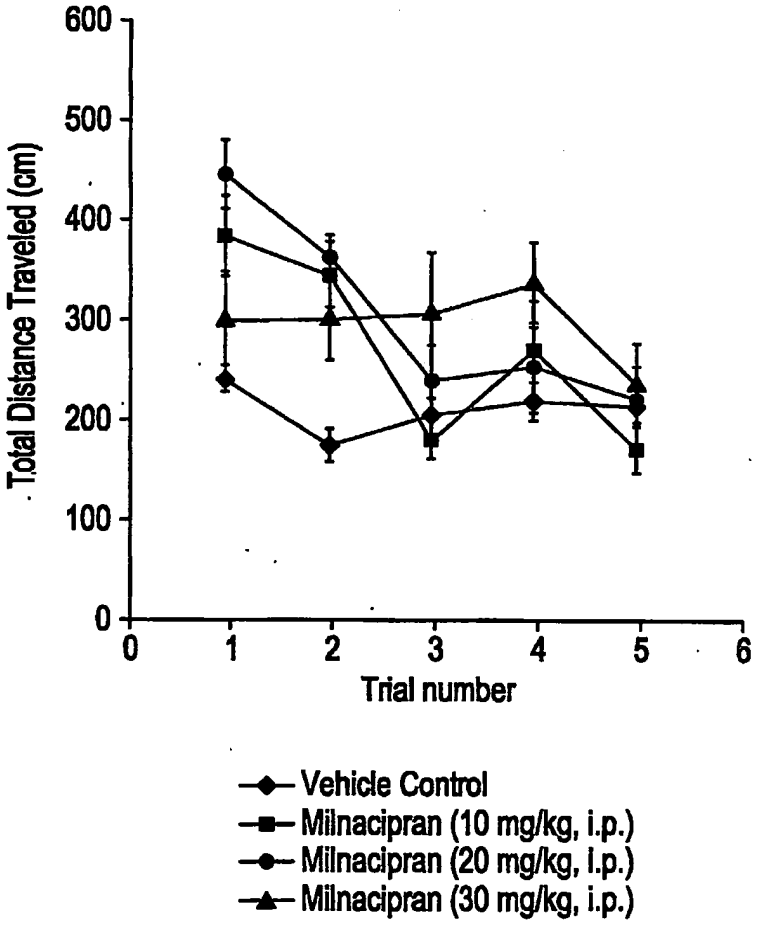
Milnacipran (20 mg/kg, i.p.)
Milnacipran (30 mg/kg, i.p.)

FIG. 2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2
3
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5
6
Trial number
Vehicle Control
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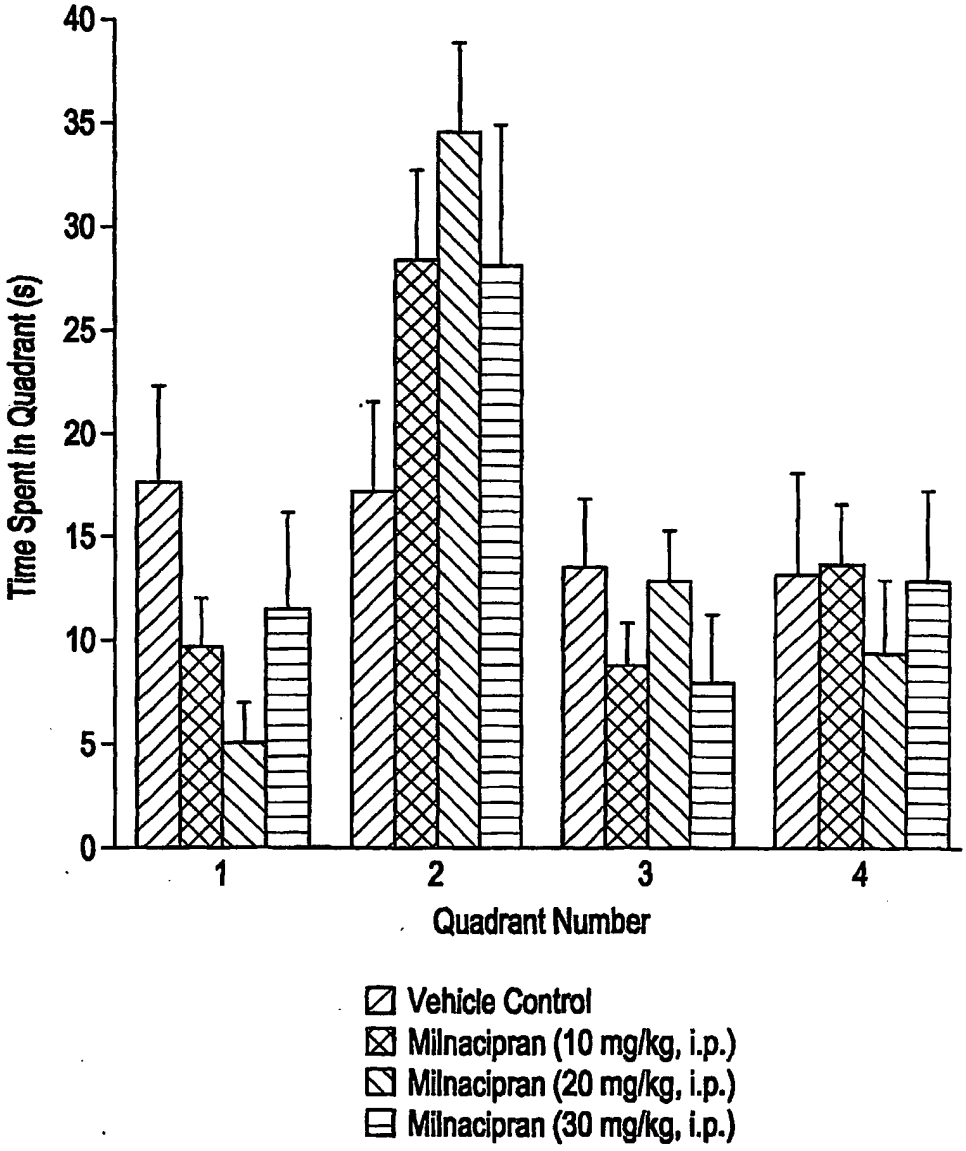
Milnacipran (20 mg/kg, i.p.)
Milnacipran (30 mg/kg, i.p.)

FIG. 3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25
20
15
10
5
0
Time Spent in Quadrant (s)
1
2
3
4
Quadrant Number
Vehicle Control
Milnacipran (10 mg/kg, i.p.)
Milnacipran (20 mg/kg, i.p.)
Milnacipran (30 mg/kg, i.p.)